Application Note AN-PAN-1060

Inline process monitoring of moisture content in tetrahydrofuran

Often, many solvents that are used daily in various manufacturing processes are not disposed of nor incinerated, but rather recovered and purified to save significant costs. Used solvents are mostly purified by distillation. Solvent recovery processes are very common in the chemical and pharmaceutical industries especially during the manufacture of Active Pharmaceutical Ingredients (APIs).

Tetrahydrofuran (THF) is one such organic solvent widely used in several industries. After THF solvent recovery, the quantification of residual water (the most common solvent impurity in THF) is an important measure for quality control in the pharmaceutical industry, for example.

This Process Application Note presents a method to accurately monitor low levels of moisture in tetrahydrofuran (THF) in «real-time» safely, reliably, and optimally with a 2060 *The* NIR Analyzer from Metrohm Process Analytics. Due to the hazardous and hygroscopic nature of THF, a single explosion-proof inline process analyzer is the preferred solution for industries to reduce chemical treatment, improve product quality, and increase profits.

INTRODUCTION

Solvents are the medium for most chemical syntheses. They aid in heat and mass transfer, facilitate separations and purifications, and act as vehicles for surface coatings, pigments, and dyes.

If they are to be disposed of after use, some harsh solvents (e.g., halogenated solvents) must be treated in a separate manner to ensure their proper disposal. Rather than going through these tedious, costly, and environmentally harmful disposal processes, many industries have become more reliant on solvent recovery, involving the collection, purification, and reuse of spent solvents.

Solvent recovery processes are very common in the chemical and pharmaceutical industries, e.g., when manufacturing Active Pharmaceutical Ingredients (APIs). To keep production processes running efficiently and to **avoid side reactions**, manufacturers must ensure that the recovered solvents are of sufficient purity for their intended purpose.

Tetrahydrofuran (THF) is a heterocyclic organic compound. Due to its high polarity and wide liquid range (-108.4 to 66 ° C), THF is a versatile solvent used extensively in many industrial processes. In the pharmaceutical industry, it is used for the fabrication of hormone and cough medicines, while in the chemical industry it is used during the manufacture of polyurethanes (e.g., polyvinyl chloride, PVC) [1].

The most common solvent impurity in THF is water. This interferes with many reactions, which is why the determination of the moisture content is crucial. Azeotropic separation is the main challenge for THF solvent recovery since this process requires more energy to break the water-THF azeotrope bond.

In many pharmaceutical processes, inline process monitoring is of vital importance to control the moisture content in various materials (**Figure 1a**). Out-of-specification water levels can impact the physical properties of pharmaceuticals, which can also negatively influence the product performance (e.g., shorter shelf life, binding errors).

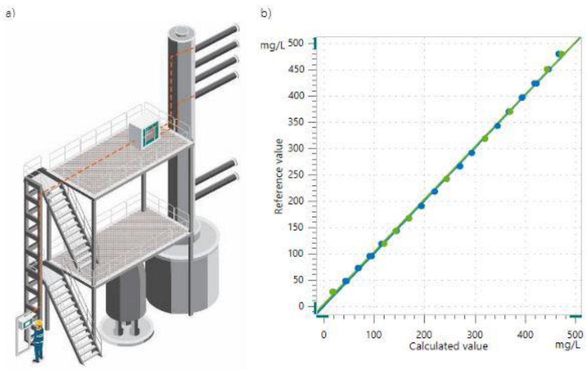

Figure 1. a) Illustration of a near-infrared spectroscopy (NIRS) system configuration for inline analysis of water content in recovered THF solvent streams. b) Correlation between the reference values from the primary method of Karl Fischer (KF) titration and the calculated values from the NIRS prediction model. Both the calibration (blue) and validation (green) data are shown.

Karl Fischer (KF) titration is generally used for moisture determination of substances in routine laboratory analysis. However, measuring the water content by this method is time-consuming and the sample is destroyed during analysis.

Manual laboratory methods can be quite cumbersome and can introduce bias depending on the analyst. Inline or online analysis of water content in recovered solvent streams gives the most precise results for high throughput API production. Near-infrared spectroscopy (NIRS) can provide a powerful alternative to manual laboratory methods for determining water in solvents. NIRS delivers results in almost «real-time» and does not require any sample preparation. Additionally, a single measurement provides information about several physical and chemical parameters so other chemicals (e.g., ethanol and isopropanol) can be monitored as well.

Metrohm Process Analytics offers analytical techniques relating to solvent characterization and qualification – near-infrared process analyzers. The 2060 *The* NIR-REx Analyzer configured for applications in ATEX areas (**Figure 2**) offers fast, reagent-free, nondestructive analysis of the water content in recovered solvents such as THF. Combination of KF titration as a reference method with NIRS enables efficient and high quality water determination even down to the mg/L (ppm) range directly in the manufacturing process.

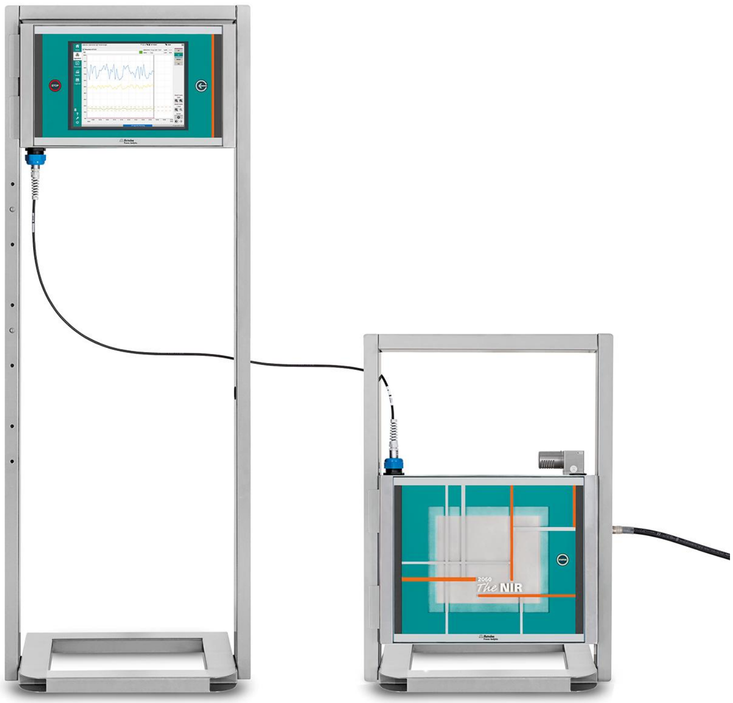

Figure 2. 2060 The NIR-REx Analyzer with fiber optic cable and probe.

APPLICATION

38 THF samples with varying moisture levels determined by KF titration ranging from 20–500 mg/L were measured with NIRS to evaluate the correlation between moisture values and changes in spectral data. 28 samples were used to develop a prediction model and 10 samples were used for external validation purposes.

NIR spectra were collected in transmission mode on a 2060 *The* NIR-REx Analyzer in the wavelength range of 1000–2250 nm using a 10 mm Hellma flow cell. The OMNIS software package was used for data acquisition, data management, and development of the quantification method (**Figure 1b** and **Table 1**).

TYPICAL RANGES

The parameters used for NIRS method development for analysis of moisture content in THF are listed in **Table 1**. A partial least squares (PLS) model using two factors shows a high correlation between the provided reference values and the calculated values ($R^2 = 0.999$) and low standard errors (**Figure 1b** and **Table 1**). Internal cross-validation was applied to verify the performance of the NIR prediction model during development.

Table 1. Parameters and results of the quantitative method development for moisture content in THF using NIRS.

Parameters	Results
Range of H_2O levels	20–500 mg/L
Regression model	PLS with 2 factors
Pretreatment	Gap-Segment
Derivative order	1
Segment size	11.5 nm
Gap size	1.5 nm
Wavelength range	1500–2000 nm
R_2	0.999
SEC	3.79 mg/L
SECV	4.01 mg/L
SEP	5.19 mg/L

REMARKS

A reference method must still be in use. An appropriate range of samples covering the process variability should be analyzed by both methods (i.e., primary reference and NIRS) to build an accurate NIRS model. Correlations are made to process specifications. The correct NIRS probe must be placed in-situ in a manner that provides sufficient sample contact with the probe tip window. Correct probe design and proper placement in process equipment is highly important.

CONCLUSION

NIRS analysis enables the comparison of «real-time» spectral data from the process to a primary method to create a simple, yet indispensable model for your process requirements. The Metrohm Process Analytics **2060 *The* NIR-REx Analyzer** can reliably measure low levels of moisture in THF streams. Additionally, it offers automated analysis results for different parts of a plant and helps to safeguard plant operations.

RELATED DOCUMENTS

AN-NIR-016 Near-infrared spectroscopy for monitoring a single-pot granulator
AN-NIR-014 Following the progress of pharmaceutical mixing studies using near-infrared spectroscopy
AN-PAN-1048 Inline moisture analysis in a pilot scale granulation process by NIRS
AN-PAN-1050 Inline moisture analysis in fluid bed dryers by near-infrared spectroscopy
WP-017 Near-infrared spectroscopy in pharmacopoeias

BENEFITS FOR NIRS IN PROCESS

- **Optimize product quality** and increase profit with fast response times for process variations
- Greater and faster **return on investment**
- **No manual sampling needed**, thus less exposure of personnel to dangerous chemicals
- **Reduced cost** of hazardous waste disposal

REFERENCES

1. *Tetrahydrofuran (THF) Market*; CH 6125; Markets and markets, 2018.

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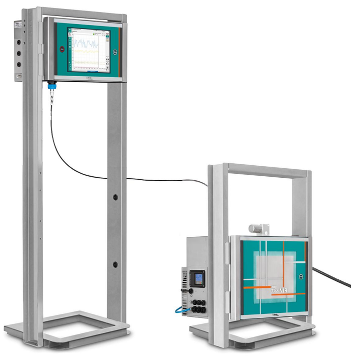
CONFIGURATION



2060 The NIR-REx Analyzer

2060 *The* NIR-REx は、Metrohm Process Analytics 製の次世代フロセス分光法措置てす。その独自て定評のある完全な設計により、*10 秒*ことに正確な結果を出します。この装置は、光ファイハーまたは接触式フローフを用いた、フロセスラインまたは反応容器における直接液体または固形物の非破壊分析を提供します。五 (5) つまてのフローフおよひ/またはフローセルを接続てきるように設計されています。弊社独自開発の多機能な組込ソフトウェアを使用して、5 つのチャンネルをすへて互いに独立して設定することかてきます。

2060 フラットフォームの一部として **2060 *The* NIR-REx Analyzer** は、光ファイハーを用いてヒューマンインターフェース (HI) と NIR キャヒネットの独自の分離を可能にします。このリモートコンフィクレーションにより、顧客嗜好とエリア区分によって異なる、工場周辺の異なる場所に二つのキャヒネットを配置することかてきます。

加えて、このアナライサーは IECEx 認証を取得し、ATEX EU 指令を満たしています。本装置は、あらゆる潜在的な爆発性ヒュームまたはカスか周囲の空気からアナライサーのカハーに入り込むのを防く、本質的な電子装置とともに、検定済みハーシ/加圧システムて設計されています。さらに、他の三つのハーションて使用可能てす：**2060 *The* NIR Analyzer**、**2060 *The* NIR-R Analyzer**、および **2060 *The* NIR-Ex Analyzer**。